

12

# EUROPEAN PATENT APPLICATION

21 Application number: 89312737.3

51 Int. Cl.<sup>5</sup>: **C07D 307/58, A61K 31/365,  
C07F 9/09**

22 Date of filing: 07.12.89

Claims for the following Contracting States: ES  
+ GR

30 Priority: 07.12.88 US 281126  
25.10.89 US 427202

43 Date of publication of application:  
13.06.90 Bulletin 90/24

64 Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI LU NL SE

71 Applicant: **ALLERGAN, INC**  
2525 Dupont Drive  
Irvine, California 92715-1599(US)

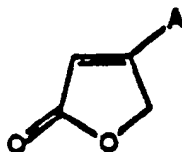
72 Inventor: Lee, Gary C. M.  
24722 Mendocino Ct.  
Laguna Hills California 92653(US)

74 Representative: Hutchins, Michael Richard et  
al  
Graham Watt & Co. London Road Riverhead  
Sevenoaks, Kent TN13 2BN(GB)

54 Anti-inflammatory 2-furanones.

57 The present invention provides compounds of the formula (I):

(I)



in which:

A is C<sub>8</sub>-C<sub>20</sub>alkyl or CH(R<sub>1</sub>)R;

R is C<sub>7</sub>-C<sub>20</sub>alkyl;

R<sub>1</sub> is hydroxy, OCOR<sub>2</sub>, 2-(methoxy)ethoxymethoxy, halogen and NHR<sub>3</sub>;

R<sub>3</sub> is H, C<sub>1</sub>-C<sub>6</sub> alkanoyl, COCF<sub>3</sub> and C<sub>1</sub>-C<sub>6</sub> sulfonyl;

R<sub>2</sub> is C<sub>1</sub>-C<sub>14</sub>alkyl or amino optionally N-substituted by one α-(C<sub>1</sub>-C<sub>4</sub>alkyl)benzyl group, by one or two C<sub>1</sub>-C<sub>4</sub>alkyl groups or by one phenyl group; or OP(R<sub>4</sub>R<sub>5</sub>); or

R is 2-(methoxy)ethoxymethoxymethyl and R<sub>1</sub> is OCO-(C<sub>7</sub>-C<sub>14</sub>alkyl); or

R is CH(OCOC<sub>1</sub>-C<sub>4</sub>alkyl)C<sub>7</sub>-C<sub>20</sub>alkyl and R<sub>1</sub> is OCO(C<sub>1</sub>-C<sub>4</sub>alkyl); and

R<sub>4</sub> = R<sub>5</sub> is H or C<sub>1</sub>-C<sub>4</sub> alkyl,

pharmaceutical compositions containing them, a process for their preparation and their use in the treatment of inflammation or an allergic response in a mammal, or psoriasis.

EP 0 372 940 A2

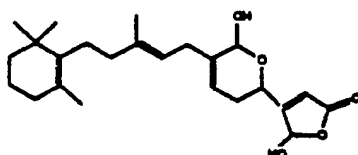
## ANTI-INFLAMMATORY 2-FURANONES

This invention relates to new 2-furanone compounds having anti-inflammatory activity, pharmaceutical compositions comprising these compounds and to methods of using them.

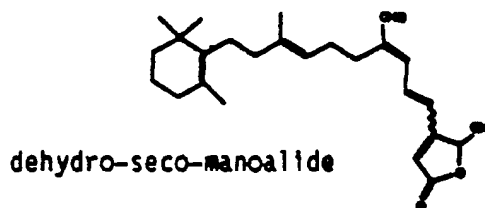
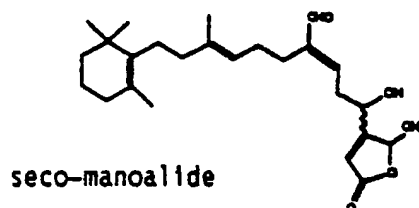
Background of the Invention

Manoalide is a furanone compound isolated from marine sponge as reported by E.D. de Silva et al., *Tetrahedron Letters* 21:1611-1614 (1980).

Anti-inflammatory, immunosuppressive and analgesic properties of manoalide are disclosed in U.S. Patent 4,447,445. Manoalide has the following structural formula:



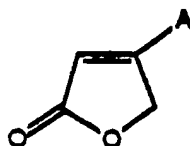
The anti-inflammatory activity of seco-manoalide and dehydro-seco-manoalide is also disclosed in U.S. Patent 4,447,445.



THE INVENTION

The compounds of the present invention are represented by the following formula:

FORMULA I



in which:

A is  $C_8-C_{20}$  alkyl or  $CH(R_1)R_2$ ;

R is  $C_7-C_{20}$  alkyl;

$R_1$  is hydroxy,  $OCOR_2$ , 2-(methoxyethoxymethoxy), halogen and  $NHR_3$ ;

5  $R_3$  is H,  $C_1-C_6$  alkanoyl,  $COCF_3$  and  $C_1-C_6$  sulfonyl;

$R_2$  is  $C_1-C_{14}$  alkyl or amino optionally N-substituted by one  $\alpha$ -( $C_1-C_4$  alkyl)benzyl group, by one or two  $C_1-C_4$  alkyl groups or by one phenyl group; or  $OP(R_4R_5)$ ; or

R is 2-(methoxyethoxymethoxymethyl) and  $R_1$  is  $OCO-(C_7-C_{14}$  alkyl); or

R is  $CH(OCOC_1-C_4 \text{ alkyl})C_7-C_{20}$  alkyl and  $R_1$  is  $OCO(C_1-C_4 \text{ alkyl})$ ; and

10  $R_4 = R_5$  is H or  $C_1-C_4$  alkyl.

Particular compounds of this invention are represented by Formula I in which:

A is  $-CH(R_1)R_2$ ;

R is  $C_7-C_{20}$  alkyl;

$R_1$  is hydroxy or  $OCOR_2$ ;

15  $R_2$  is  $C_1-C_{14}$  alkyl or  $\alpha$ -methylbenzylamino; or

R is 2-(methoxyethoxymethoxymethyl) and  $R_1$  is  $OCO-(C_7-C_{14}$  alkyl).

Specific compounds of this invention are, for example:

4-[1-dodecanoyloxy-2-(2-methoxyethoxy)methoxymethyl]-2(5H)-furanone,

4-(1-acetoxytridecyl)-2(5H)-furanone,

20 4-[1-((R)-(+)- $\alpha$ -methylbenzylcarbamoyl)tridecyl]-2(5H)-furanone, and

4-(1-hydroxytridecyl)-2(5H)-furanone.

Certain of the compounds of this invention contain chiral centers and accordingly, may be prepared as enantiomeric or diastereomeric mixtures or in optically pure form. Unless otherwise specified herein, such preparations are racemates at each chiral center. However, the scope of the invention is not to be  
25 considered as limited to these forms but also to encompass the individual optical isomers of the compounds.

Compounds of the invention are prepared by procedures which are illustrated hereinbelow and described in more detail in the examples.

30

35



According to the above procedure, a 5-hydroxy-2(5H)-furanone is treated with a reducing agent, such as sodium borohydride, to give compounds of Formula I.

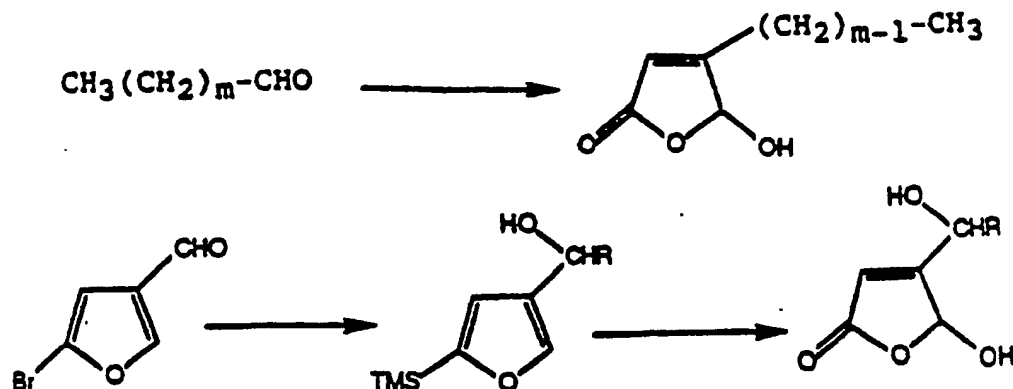
40 Alternatively, compounds of Formula I in which  $R_1$  is  $OCOR_2$  are prepared from compounds of Formula I in which  $R_1$  is hydroxy by acylating with an acyl anhydride or halide.

The 5-hydroxy-2(5H)-furanone starting materials for the compounds of this invention are prepared by procedures which are illustrated hereinbelow and described in more detail in the examples.

45

50

55



According to procedure I, an aldehyde is reacted with glyoxylic acid and phosphoric acid to give a 4-alkyl-5-hydroxy-2(5H)-furanone.

In procedure II, 5-bromo-3-furaldehyde is reacted with a Grignard reagent (RMgX) and the resulting mixture is treated with *t*-butyl lithium and trimethylsilyl chloride to give a 4-[R-CH(OH)]-2-trimethylsilylfuran. Also, the aldehyde group of 5-trimethylsilyl-3-furaldehyde may be reacted with 2-(methoxy)ethoxymethyl tributylstannylmethyl ether and the OH group O-alkanoylated. The 4-substituted-2-trimethylsilylfuran intermediates are oxidized using Rose Bengal as an initiator and irradiating to give the 4-substituted-5-hydroxy-2(5H)-furanones.

The intermediates for the compounds of Formula I in which A is CH(OCOC<sub>1</sub>-C<sub>4</sub>)-(C<sub>7</sub>-C<sub>20</sub>alkyl) are prepared by converting the aldehyde group of 5-trimethylsilyl-3-furaldehyde to a vinyl group, for example by Wittig reaction with an alkyl triphenylphosphonium bromide/butyl lithium, oxidizing the vinyl group using, for example, osmium tetroxide, then O-alkanoylating.

The 4-[R-CH(R<sub>1</sub>)]-2-trimethylsilylfuran is converted to the corresponding 4-substituted 5-hydroxy-2(5H)-furanone by treating with oxygen and irradiating using an initiator such as Rose Bengal.

5-Trimethylsilyl-3-furaldehyde may be prepared by brominating 3-furaldehyde to give 5-bromo-3-furaldehyde which is converted to the dimethylacetal, then treated with *t*-butyl lithium and trimethylsilyl chloride.

A preferred method for preparing 5-trimethylsilyl-3-furaldehyde is by reacting lithium morpholide with 5-bromo-3-furaldehyde to protect the aldehyde group, then reacting with *t*-butyl lithium and trimethylsilyl chloride to give 5-trimethylsilyl-3-furaldehyde.

An improved method for preparing 5-trimethylsilyl-3-furaldehyde consists of reacting lithium morpholide with 3-furaldehyde, followed by secondary-butyl lithium, followed by trimethylsilyl chloride. This method is also advantageous for the preparation of 5-triethylsilyl-3-furaldehyde using triethylsilyl chloride. 5-Triethylsilyl-3-furaldehyde is useful as an intermediate in place of the trimethyl compound in methods described herein for preparing compounds of this invention.

In addition, this invention relates to pharmaceutical compositions containing the compounds of Formula I as active ingredients and to methods of using the compounds and pharmaceutical compositions of this invention to produce anti-inflammatory, immunosuppressant and anti-proliferative activity. These compounds are useful in treating inflammation, in suppressing unwanted immune responses and in retarding proliferation of cells. Uses include treatment of rheumatoid arthritis, osteoarthritis, rheumatic carditis and autoimmune diseases such as allergic diseases, bronchial asthma and myasthenia gravis and ocular and dermal inflammatory diseases. The compounds are useful in treating psoriasis, acne, atopic diseases and allergic conjunctivitis. They are also useful as adjuvant therapy associated with organ and tissue transplants.

The activity of the compounds of this invention is demonstrated by the effect on calcium homeostasis. The compounds are calcium channel antagonists. This activity is shown by effect on intracellular calcium levels in experiments using gastric glands, spleen cells, epithelial cells, GH<sub>3</sub> cells, etc. Calcium is inhibited from entering through the plasma membrane calcium channels and calcium release from intracellular stores is also blocked. Modification of calcium homeostasis is expected to have application in diseases of the nervous system involving modification of membrane lipids or transmitter release (Parkinson's, Alzheimer's), diseases of the cardiovascular system involving application of cardiac or vascular smooth muscle contractility and platelet aggregation (hypertension, cardiac infarction and atherosclerosis), diseases of the gastrointestinal tract such as ulcer disease, diarrhea, motility due to secretion of acid or Cl<sup>-</sup>, diseases of the kidney involving renal handling of fluid and electrolytes (metabolic acidosis, alkalosis), and disease of abnormal growth (neoplasia, psoriasis).

The compounds of this invention differ from manoalide in that they demonstrate weak or no activity as inhibitors of the enzyme phospholipase A<sub>2</sub> *in vitro* or of phosphoinositide-specific phospholipase C.

The compounds are active in reducing inflammation in the mouse ear anti-inflammatory assay *in vivo*.

The compounds of this invention, like manoalide, appear to be devoid of the endocrine properties of the glucocorticoids while having anti-inflammatory and immunosuppressive properties.

In the methods of this invention, the compounds of the invention are administered to mammals, including humans, in an effective amount to produce the desired activity, preferably in an amount of about 0.05 to 100 mg per day per kilogram of body weight. The amount of the compound depends upon the disease or condition being treated, the severity thereof, the route of administration and the nature of the host. The compounds may be administered topically, orally, parenterally or by other standard routes of administration.

Pharmaceutical compositions of this invention comprise compounds of Formula I and pharmaceutical carriers suitable for the route of administration. Standard methods for formulating pharmaceutical compositions of this type may be found in Remington's Pharmaceutical Sciences, Mack Publishing Company,

Easton, PA.

For topical administration, the pharmaceutical composition may be in the form of a salve, cream, ointment, spray, powder or the like. Standard pharmaceutical carriers for such compositions may be used. Preferably, compositions for topical administration will contain 0.05-5% of the active ingredient.

5 A typical cream formulation may contain the following:

	Ingredient	Parts by Weight
10	Water/glycol mixture (15% or more glycol)	50-99
	Fatty alcohol	1-20
	Non-ionic surfactant	0-10
	Mineral oil	0-10
	Typical pharmaceutical adjuvants	0-5
15	Active ingredient	0.05-5

A typical ointment formulation may contain the following:

	Ingredients	Parts by Weight
20	White petrolatum	40-94
	Mineral oil	5-20
25	Glycol solvent	1-15
	Surfactant	0-10
	Stabilizer	0-10
	Active ingredient	0.05-5

30

For oral administration, suitable pharmaceutical carriers include mannitol, lactose, starch, magnesium stearate, talcum, glucose and magnesium carbonate. Oral compositions may be in the form of tablets, capsules, powders, solutions, suspensions, sustained release formulations, and the like.

35 A typical tablet or capsule may contain the following:

	Ingredients	Percent w/w
40	Lactose, spray-dried	40-99
	Magnesium stearate	1-2
	Cornstarch	10-20
	Active ingredient	0.001-20

45

Parenteral compositions are prepared in conventional suspension or solution forms, as emulsions or as solid forms for reconstruction. Suitable carriers are water, saline, dextrose, Hank's solutions, Ringer's solution, glycerol, and the like. Parenteral administration is usually by injection which may be subcutaneous, intramuscular or intravenous.

50

The compounds of this invention may be combined with other known anti-inflammatory/immunosuppressive agents such as steroids or non-steroidal anti-inflammatory agents (NSAID) in the pharmaceutical compositions and methods described herein.

The following examples are intended to illustrate the invention but are not limiting. All temperatures are in degrees Centigrade. NMR data are recorded in delta ppm.

55

#### Example 1

5-Trimethylsilyl-3-furaldehyde

n-Butyl lithium (a 1.6 M solution in hexane; 31.0 ml, 49.7 mmol) was added dropwise to a solution of morpholine (4.33 ml, 49.7 mmol; freshly distilled from barium oxide) in tetrahydrofuran at -78° under argon. After 15 minutes, a solution of 5-bromo-3-furaldehyde (7.5 g, 49.7 mmol) in tetrahydrofuran (THF) was added dropwise. Stirring was continued for 30 min. and n-butyl lithium (a 1.6 M solution in hexane; 46.6 ml, 74.5 mmol) was added dropwise. After 1 hour at -78°, chlorotrimethylsilane (18.9 ml, 149 mmol) was added and stirring continued while the cooling bath attained room temperature. The reaction mixture was quenched with 10% hydrochloric acid and the phases were separated. The aqueous phase was stirred, in the presence of ethyl ether (30 ml), with 10% hydrochloric acid at 0° C for 1/2 hour. The organic phases were combined, washed (brine), dried (magnesium sulfate) and evaporated down. The residue was distilled under vacuum to give the title aldehyde as a colorless oil b.p. 48-50°/0.25 torr.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.29 (5.9H), 6.98 (5.1H), 8.25 (5.14) and 9.95 (5.1H)

<sup>13</sup>C NMR (CDCl<sub>3</sub>): -2.0, 116.2, 128.9, 155.3, 164.1 and 184.5.

MS m/e: Exact mass calculated for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>S: 168.0607, found 168.0588.

Example 2Alternative preparation of 5-trimethylsilyl-3-furaldehyde

n-Butyl lithium (a 2.5 M solution in hexane; 28.8 ml, 72 mmol) was added to a solution of morpholine (6.28 ml, 72 mmol) in tetrahydrofuran (700 ml) at -78° under argon. After 20 minutes, 3-furaldehyde (7.0 g, 72 mmol) was added. After another 20 minutes, sec-butyl lithium (a 1.3 M solution in cyclohexane; 55.4 ml, 72 mmol) was added dropwise and stirring continued at -78° for 7 hours before trimethylsilyl chloride (27 ml, 2.6 mmol) was added. Stirring was continued overnight (14 hours) while the cooling bath was allowed to attain room temperature. The solution was poured into ice cold 10% (v/v) hydrochloric acid (200 ml) and after stirring at 0° for 10 minutes, the layers were separated. The aqueous phase was extracted with ethyl ether. All the organic phases were combined, dried (magnesium sulfate) and evaporated down to give a light brown oil, which was purified by flash chromatography on silica using 2% ethyl ether/hexane. Fractions with R<sub>f</sub> of about 0.30 (silica, 10% ethyl ether/hexane) on evaporation gave the title aldehyde as a light yellow oil, b.p. 48-50°/0.25 torr.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.29 (s, 9H), 6.98 (s, 1H), 8.25 (s, 1H) and 9.95 (s, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): -2.0, 116.2, 128.9, 155.3, 164.1 and 184.5.

Example 34-(1-Hydroxytridecyl)-2-trimethylsilylfuran

A solution of 5-trimethylsilyl-3-furaldehyde (0.5 g, 2.97 mmol) in tetrahydrofuran (5 ml) was added to a solution of dodecyl magnesium bromide (5.95 mmol; prepared from 1.48 g dodecyl bromide and 146 mg magnesium turnings in 30 ml tetrahydrofuran) at room temperature. After 2 hours, the mixture was quenched with ammonium chloride solution and extracted thoroughly with ethyl ether. Evaporation of the dried (magnesium sulfate) extracts gave an oil which was flash chromatographed on silica using 10% ethyl ether/hexane. Fractions with R<sub>f</sub> about 0.13 on evaporation gave the title alcohol as a pale yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.26 (s, 9H), 0.89 (t, 3H, J = 7.3 Hz), 1.27 (broad s, 16H), 1.62 (br, 1H), 1.75 (m, 2H), 4.65 (t, 1H, J = 6.8 Hz), 6.63 (s, 1H) and 7.57 (s, 1H).

MS m/e (% abundance): 293 (M<sup>+</sup> -OH, 2), 221 (5), 177 (31), 175 (33), 97 (14), 87 (10), 85 (64), 83 (100), 73 (14) and 57 (12).

4-(1-Hydroxytridecyl)-5-hydroxy-2(5H)-furanone

A mixture of 4-(1-hydroxytridecyl)-2-trimethylsilylfuran (271.2 mg, 0.8 mmol) and Rose Bengal (5 mg) in tetrahydrofuran (10 ml) was exposed to singlet oxygen for 2 hours at  $-78^{\circ}$ . The residue, after solvent removal, was flash chromatographed on silica using 70% ethyl ether/petroleum ether. Fractions with  $R_f$  of about 0.09 (60% ethyl ether/petroleum ether) on evaporation afforded the captioned furanone as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.91 (t, 3H,  $J=6.8$  Hz), 1.29-1.34 (broad m, 20H), 1.75 (m, 2H), 4.00 (br, 2H, exchanged with  $\text{D}_2\text{O}$ ), 4.68 (m, 1H), 5.99 (s, 1H), 6.10 (d, 1H,  $J=7.5$  Hz, sharpened into a singlet on  $\text{D}_2\text{O}$  exchange), 6.15 (d, 1H, sharpened into a singlet on  $\text{D}_2\text{O}$  exchange) and 6.28 (s, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.1, 22.7, 25.1, 25.1, 25.7, 29.1, 29.3, 29.5, 29.6, 29.6, 29.8, 31.9, 35.3, 35.6, 68.0, 68.2, 97.5, 97.6, 117.6, 118.1, 168.9, 170.4, 170.6 and 170.9.

MS  $m/e$ : exact mass calculated for  $\text{C}_{17}\text{H}_{31}\text{O}_4$  ( $M + \text{H}^+$ ) 299.2222, found 299.2231.

4-(1-Hydroxytridecyl)-2(5H)-furanone

Sodium borohydride (68.0 mg, 1.8 mmol) was added to a solution of 4-(1-hydroxytridecyl)-5-hydroxy-2(5H)-furanone (268 mg, 0.9 mmol) in tetrahydrofuran (5 ml) and methanol (5 drops) at room temperature. After 5 hours, the mixture was quenched with dilute hydrochloric acid and extracted with ethyl acetate (discarded). The aqueous phase was evaporated to near dryness, saturated with sodium chloride and extracted thoroughly with ethyl acetate. Evaporation of the dried (magnesium sulphate) extracts gave an oil, which was purified by preparation TLC (silica plate; developed with 60% ethyl ether/hexane). The title furanone was obtained as an off-white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.91 (t, 3H,  $J=6.4$  Hz), 1.28 (brs, 20H), 1.70 (m, 2H), 4.66 (t, 1H,  $J=7.5$  Hz), 4.90 (brs, 2H) and 5.98 (brs, 1H).

$^{13}\text{C}$  NMR (mixtures of diastereomers) ( $\text{CDCl}_3$ ): 14.0, 22.6, 25.0, 25.2, 25.4, 29.2, 29.4, 29.5, 31.4, 31.8, 35.1, 35.4, 36.2, 40.8, 62.5, 68.4, 70.1, 71.2, 71.4, 72.2, 83.2, 114.3, 173.9 and 174.4.

MS  $m/e$ : exact mass calculated for  $\text{C}_{17}\text{H}_{30}\text{O}_3$  ( $M^+$ ) 282.2194, found 282.2187.

Example 44-(1-Acetoxytridecyl)-2(5H)-furanone

A mixture of 4-(1-hydroxytridecyl)-2(5H)-furanone (62 mg, 0.22 mmol), acetic anhydride (1/2 ml), pyridine (1/2 ml) and tetrahydrofuran (2 ml) was stirred at room temperature for 14 hours. After most of the solvent was removed under high vacuum, the residue was purified by preparative TLC (silica plate; 60% ethyl ether/hexane). The title furanone was obtained as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.89 (t, 3H,  $J=6.3$  Hz), 1.26 (brs, 20H), 1.80 (m, 2H), 2.09 (s, 3H), 2.14 (s, 3H), 4.82 (dd, 2H,  $J=15.0$  Hz), 5.65 (t, 1H,  $J=7.5$  Hz) and 5.98 (brs, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.0, 20.7, 20.8, 22.5, 22.6, 24.8, 24.9, 25.1, 25.3, 29.1, 29.3, 29.4, 29.6, 31.0, 31.7, 31.8, 32.2, 33.5, 35.0, 38.7, 39.7, 64.1, 69.2, 69.7, 70.8, 73.8, 82.6, 116.2, 167.7, 169.9 and 172.8.

MS  $m/e$ : Exact mass calculated for  $\text{C}_{19}\text{H}_{32}\text{O}_4$  ( $M +$ ) 324.2300, found 324.2296.

Example 55-Bromo-3-furaldehyde

3-Furaldehyde (11.6 g, 121 mmol) was added dropwise to a solution of anhydrous aluminum bromide (48.1 g, 180 mmol) in dry dibromomethane (200 ml). An exothermic reaction ensued and a dark brown color developed. After 10 minutes, bromine (6.82 ml, 133 mmol) was added dropwise and the mixture was warmed at approximately 50° for 1 hour. On cooling, the mixture was poured into crushed ice and the organic layer was separated. The aqueous phase was extracted with methylene chloride. All the organic layers were combined, washed (successively with water, 5% aqueous sodium bicarbonate and brine) and filtered through celite. Distillation of the dried (magnesium sulfate) extract gave 5-bromo-3-furaldehyde as a colorless oil: bp 55°/0.25 torr.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.80 (s, 1H), 8.10 (s, 1H) and 9.91 (s, 1H).

#### 4-(1-Hydroxynonyl)-2-trimethylsilylfuran

A mixture of 1-bromooctane (1.33 g, 6.9 mmol) and magnesium turnings (174 mg, 7.3 mmol) in tetrahydrofuran (8 ml) was refluxed under argon for 60 minutes. After cooling to 0°, a solution of 5-bromo-3-furaldehyde (1.21 g, 6.9 mmol) in THF (1 ml) was added and conditions maintained for 60 min. The mixture was further cooled to -78° and *tert*-butyl lithium (a 1.7M solution in pentane, 4.26 ml, 7.3 mmol) was added dropwise, followed by chlorotrimethylsilane (2.63 ml, 20.7 mmol) after 1 hour. Stirring was continued overnight while the cooling bath attained room temperature. The mixture was quenched with saturated aqueous ammonium chloride, diluted with water (15 ml) and extracted with ether. Evaporation of the dried (magnesium sulfate) extract gave a brown oil, which was subjected to flash chromatography on silica using 15% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> of about 0.2 on evaporation gave the captioned compound as a yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.32 (s, 9H), 0.94 (t, 3H, J=7.3 Hz), 1.33 (broad s, 12H), 1.70 (br, 1H), 1.85 (m, 2H), 4.71 (t, 1H, J=6.8 Hz), 7.32 (s, 1H) and 7.63 (s, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): -1.70, 14.0, 22.6, 25.4, 25.6, 25.7, 29.2, 29.5, 31.8, 36.8, 37.6, 37.9, 66.7, 66.9, 110.2, 118.3, 129.2, 140.4, 143.4 and 161.2.

MS m/e (% abundance): 282 (M<sup>+</sup>, 2), 265 (3), 249 (4), 247 (4), 182 (3), 177 (11), 175 (12), 169 (9), 167 (3) and 147 (5); exact mass calculated for C<sub>16</sub>H<sub>30</sub>SiO<sub>2</sub> 282.2015, found 282.2009.

#### 4-(1-Acetoxynonyl)-2-trimethylsilylfuran

A mixture of 4-(1-hydroxynonyl)-2-trimethylsilylfuran (1.65 g, 5.9 mmol), acetic anhydride (2 ml) and pyridine (3 ml) was stirred under argon at approximately 20° for 17 hours. After most of the solvent was removed under high vacuum (less than 40° C), the residue was dissolved in ether (40 ml) and washed thoroughly with aqueous copper sulfate and water. Drying (magnesium sulfate) and evaporation gave a brown oil, which was flash chromatographed on silica using 5% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> 0.32 on evaporation afforded 4-(1-acetoxynonyl)-2-trimethylsilylfuran as a pale yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.26 (s, 9H), 0.89 (t, 3H, J=7.6 Hz), 1.27 (broad s, 12H), 1.90 (m, 2H), 2.06 (s, 3H), 5.78 (t, 1H, J=6.7 Hz), 6.60 (s, 1H) and 7.61 (s, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): -1.73, 14.0, 21.1, 21.2, 22.6, 25.3, 25.5, 29.2, 29.2, 29.4, 31.8, 34.4, 34.8, 68.0, 68.3, 68.6, 110.5, 118.6, 125.0, 141.8, 144.4, 161.1 and 170.4.

MS m/e (% abundance): 325 (M<sup>+</sup>+1, 5), 324 (21), 283 (13), 282 (56), 265 (16), 183 (27), 170 (36), 169 (41), 154 (14), 153 (13), 117 (32) and 73 (100); Exact mass calculated for C<sub>18</sub>H<sub>32</sub>SiO<sub>3</sub> 324.2121, found 324.2115.

#### 4-(1-Acetoxynonyl)-5-hydroxy-2(5H)-furanone

A mixture of 4-(1-acetoxynonyl)-2-trimethylsilylfuran (323 mg, 0.9 mmol) and Rose Bengal (5 mg) in THF (10 ml) was exposed to singlet oxygen for 5.5 hours at -78°. The residue, after solvent removal, was flash chromatographed on silica using 60% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> 0.13 on evaporation afforded the captioned compound as a colorless solid, mp 54-5°.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.96 (t, 3H, J=6.7 Hz), 1.34 (broad s, 12H), 1.89 (m, 2H), 2.20 (s, 3H), 2.21 (s, 3H),



4.54 (d, 1H, J=7.6 Hz, exchanged with D<sub>2</sub>O), 5.12 (d, 1H, J=10.5 Hz, exchanged with D<sub>2</sub>O), 5.47 (t, 1H, J=6.3 Hz), 5.55 (t, 1H, J=6.3 Hz), 6.06 (2d + s) and 6.26 (d, 1H, J=7.3 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 14.0, 20.8, 22.6, 24.9, 25.0, 29.1, 29.3, 31.7, 32.9, 33.0, 69.3, 69.8, 98.0, 98.2, 118.3, 119.0, 166.7, 167.1, 170.0 and 171.1.

5 MS m/e: exact mass calculated for C<sub>15</sub>H<sub>24</sub>O<sub>5</sub> 284.1624, found 284.1691.

#### 4-(1-Acetoxyonyl)-2(5H)-furanone

10

Sodium borohydride (12.9 mg, 0.34 mmol) was added to a solution of 4-(1-acetoxyonyl)-5-hydroxy-2-(5H)-furanone (48.1 mg, 0.17 mmol) in tetrahydrofuran (5 ml) and methanol (0.5 ml) at room temperature. After 40 minutes, most of the solvent was removed and water (5 ml) was added. Extraction (dichloromethane) and evaporation of the dried (magnesium sulphate) extracts gave a residue, which was

15

flash chromatographed on silica using 60% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> of about 0.40 on evaporation afforded the title furanone as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.95 (brt, 3H), 1.33 (brs, 12H), 1.83 (m, 2H), 2.19 (s, 3H), 4.83 (d, 1H, J=15.0 Hz), 4.91 (d, 1H, J=15.0 Hz), 5.69 (brt, 1H) and 6.03 (s, 1H).

20

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 14.0, 20.7, 22.6, 24.8, 29.1, 29.3, 31.7, 33.5, 69.8, 70.8, 116.3, 167.7, 170.0 and 172.8.

MS m/e: exact mass calculated for C<sub>15</sub>H<sub>24</sub>O<sub>4</sub> (M<sup>+</sup>) 268.1675, found 268.1678.

#### Example 6

25

#### 4-[1-((R)-(+)-α-Methylbenzylcarbamoyl)tridecyl]-2(5H)-furanone

30

A solution of (R)-(+)-α-methylbenzyl isocyanate (31 mg, 0.21 mmol) in tetrahydrofuran (1 ml) was added to a solution of 4-(1-hydroxytridecyl)-2(5H)-furanone (20 mg, 0.07 mmol) and triethylamine (30 μl, 0.21 mmol) in tetrahydrofuran (1 ml) at room temperature. Stirring was continued for 2 days and the mixture was quenched with water. Extraction (dichloromethane) and evaporation of the dried (magnesium sulphate) extracts gave an oil, which was purified by preparative TLC (silica plate; developed with 60% ethyl ether/hexane). The title furanone was isolated as low melting colorless plates.

35

<sup>1</sup>H NMR (mixture of diastereomers) (CDCl<sub>3</sub>): 0.94 (t, 3H, J=7.1 Hz), 1.31 (brs, 20H), 1.45 (d, 3H, J=6.9 Hz), 1.70 (m, 2H), 4.40 (m, 1H), 4.70 (m, 2H), 4.91 (brs, 2H), 6.00 (brs, 1H) and 7.25 (m, 5H).

40

<sup>13</sup>C NMR (mixture of diastereomers) (CDCl<sub>3</sub>): 14.1, 22.7, 23.4, 25.0, 25.5, 29.3, 29.5, 29.6, 31.3, 31.9, 35.7, 36.5, 41.0, 50.3, 68.8, 70.0, 71.0, 72.6, 76.4, 114.9, 125.7, 125.9, 127.2, 127.4, 128.6, 128.7, 144.0 and 172.4.

MS m/e (% abundance): 283(M<sup>+</sup>-C<sub>9</sub>H<sub>16</sub>NO, 43), 237(70), 131(100) and 91(72).

45

#### EXAMPLE 7

#### 2-Methoxyethoxymethyl tributylstannylmethyl ether

50

Tributyltin hydride (2.69 ml, 0.01 mol) was added dropwise to a solution of lithium diisopropylamide (a 1.5 M solution in cyclohexane; 6.7 ml, 0.01 mol) in tetrahydrofuran (20 ml) at 0° under argon. After 15 minutes, paraformaldehyde (300 mg, 0.01 mol) was added, followed by 2-methoxyethoxymethyl chloride

55

(1.15 ml, 0.01 mol) after 3 hours. Stirring was continued at room temperature for 12 hours and the mixture was quenched with water. Extraction (ethyl ether) and evaporation of the dried (magnesium sulphate) extracts gave an oil, which was flash chromatographed on silica using 5% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> of about 0.24 on evaporation afforded the desired ether as a colorless oil (1.11 g, 27%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 0.92 (m, 15H), 1.35 (m, 6H), 1.55 (m, 6H), 3.44 (s, 3H), 3.60 (m, 2H), 3.70 (m, 2H), 3.80 (dd, 2H), and 4.64 (s, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) 8.7, 13.5, 27.1, 28.8, 57.5, 58.8, 66.3, 71.7 and 87.4.

MS m/e (% abundance) 428 ((M + NH<sub>4</sub>)<sup>+</sup>, 8), 353(100) and 296(81).

5

#### 4-[1-Dodecanoyloxy-2-(2-methoxyethoxy)methoxyethyl]-2-trimethylsilylfuran

10 n-Butyl lithium (a 1.6 M solution in hexane; 0.74 ml, 1.18 mmol) was added to a solution of 2-methoxyethoxy-methyl tributylstannylmethyl ether (481.6 mg, 1.18 mmol) in tetrahydrofuran (5 ml) at -78° under argon. After 10 minutes, a solution of 5-trimethylsilyl-3-furaldehyde (198 mg, 1.18 mmol) was added, followed by lauroyl chloride (0.26 ml, 1.18 mmol) after 20 minutes. Stirring was continued at room temperature for 48 hours and the mixture was quenched with water. Extraction (ether) and evaporation of  
15 the dried (magnesium sulphate) extracts gave an oil, which was flash chromatographed on silica using 20% ethyl ether/petroleum ether. Fractions with R<sub>f</sub> of about 0.27 (30% ethyl ether/petroleum ether) on evaporation afforded the title ester as a pale yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.26 (s, 9H), 0.89 (t, 3H, J = 6.9 Hz), 1.27 (brs, 16H), 1.65 (m, 2H), 2.34 (t, 2H, J = 7.7 Hz), 3.41 (s, 3H), 3.58 (m, 2H), 3.67 (m, 2H), 3.84 (m, 2H), 4.77 (s, 2H), 6.05 (dd, 1H, J = 7.5 Hz, 3.8 Hz),  
20 6.62 (s, 1H) and 7.66 (s, 1H).

MS m/e (% abundance): 488 ((M + NH<sub>4</sub>)<sup>+</sup>, 26), 271 (100), 195 (42), 123 (25) and 90 (18).

#### 4-[1-Dodecanoyloxy-2-(2-methoxyethoxy)methoxyethyl]-5-hydroxy-2(5H)-furanone

25

A mixture of 4-[1-dodecanoyloxy-2-(2-methoxyethoxy)methoxyethyl]-2-trimethylsilylfuran (229 mg, 0.49 mmol) and Rose Bengal (5 mg) in tetrahydrofuran (7 ml) was exposed to singlet oxygen for 2 hours at -78°. The residue, after solvent removal, was purified by preparative TLC (silica plate; developed with 80% ethyl ether/petroleum ether). The title ester was obtained as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.89 (t, 3H, J = 6.9 Hz), 1.27 (brs, 16H), 1.65 (brt, 2H), 2.43 (t, 2H, J = 7.8 Hz), 3.40 (s, 3H), 3.05 (m, 2H), 3.30 (m, 2H), 3.95 (m, 2H), 4.74 (s, 2H), 5.70 (brm, 1H), 6.11 (s, 1H) and 6.14 (s, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 14.1, 22.7, 24.8, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 34.0, 58.9, 67.2, 67.4, 68.5, 71.7, 95.6, 97.9, 98.1, 120.2, 169.6 and 172.9.

35 MS m/e: exact mass calculated for C<sub>22</sub>H<sub>42</sub>NO<sub>5</sub>(M + NH<sub>4</sub>)<sup>+</sup> 448.2910, found 449.2890.

#### 4-[1-Dodecanoyloxy-2-(2-methoxyethoxy)methoxyethyl]-2(5H)-furanone

40

A mixture of 4-[1-dodecanoyloxy-2-(2-methoxyethoxy)methoxyethyl]-5-hydroxy-2(5H)-furanone (31.8 mg, 73.9 μmol) and sodium borohydride (5.6 mg, 0.15 mmol) in tetrahydrofuran (2 ml) containing methanol (5 drops) was stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with dichloromethane. The residue, after solvent removal, was purified by preparative TLC (silica plate;  
45 developed with 60% ethyl ether/petroleum ether). The title furanone was obtained as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.92 (t, 3H, J = 6.0 Hz), 1.30 (brs, 16H), 1.75 (brm, 2H), 2.41 (t, 2H, J = 7.6 Hz), 3.43 (s, 3H), 3.60 (m, 2H), 3.70-3.90 (m, 4H), 4.45 (brm, 2H), 4.77 (brs, 2H), 5.50 (brt, 1H) and 6.05 (br, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 14.1, 22.7, 24.8, 29.0, 29.2, 29.3, 29.4, 29.6, 31.9, 34.0, 34.3, 58.5, 58.9, 59.0, 66.9, 67.4, 67.7, 68.5, 71.4, 71.6, 95.5, 95.6, 117.2, 165.4 and 172.5.

50 MS m/e (% abundance): 432 ((M + NH<sub>4</sub>)<sup>+</sup>, 43), 415 (M<sup>+</sup> + 1, 10), 326 (9), 232 (38), 215 (100), 128 (41), 123 (12), 106 (16), 94 (36) and 89 (29).

### Example 8

55

#### 5-Hydroxy-4-octyl-2(5H)-furanone

A mixture of decyl aldehyde (10 g, 64 mmol), glyoxylic acid monohydrate (5.6 g, 61 mmol) and 85% phosphoric acid (10 ml) was warmed at approximately 80° for 24 hours. On cooling, the solution was diluted with ethyl ether/dichloromethane (1:1, 50 ml each) and washed thoroughly with brine (5 times). The organic layer was dried (magnesium sulfate), evaporated down and purified by flash chromatography on silica using 40% ethyl acetate/hexane as eluant. Fractions with  $R_f$  of about 0.14 on evaporation afforded the title furanone contaminated with the ring-opened form. The mixture was used directly in the next stage.

10

#### 4-Octyl-2(5H)-furanone

Sodium borohydride (318 mg, 8.4 mmol) was added to 5-hydroxy-4-octyl-2(5H)-furanone (590 mg, 2.8 mmol) in tetrahydrofuran (5 ml) and methanol (1 ml) at room temperature. After 2 hours stirring, most of the solvent was removed and water (10 ml) was added. Extraction (dichloromethane) and evaporation of the dried (magnesium sulphate) extracts gave a residue, which was purified by preparative TLC (silica plate, developed with 60% ethyl ether/petroleum ether). The title furanone was obtained as a colorless solid: mp 65-66°.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.86 (brt, 3H), 1.25 (brs, 10H), 1.45 (m, 2H), 2.51 (m, 2H), 4.21 (brs, 2H) and 5.98 (s, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.1, 22.7, 28.9, 29.2, 29.3, 29.7, 29.9, 31.9, 65.8, 112.5, 165.8 and 170.6.

MS m/e: Exact mass calculated for  $\text{C}_{12}\text{H}_{20}\text{O}_2$  ( $M^+$ ) 196.1463, found 196.1468.

25

#### Example 9

Triethylamine (0.55 ml, 3.95 mmol), followed by oxalyl chloride (0.34 ml, 3.95 mmol) was added dropwise to a solution of 3-(1-hydroxytridecyl)-5-trimethylsilylfuran (890 mg, 2.63 mmol) in anhydrous dichloromethane (10 ml) at 0°. After 40 minutes, the reaction was quenched with ice water. Extraction (dichloromethane) and evaporation of the dried (magnesium sulfate) extracts gave an oil, which was purified by flash chromatography on silica using 5% ethyl ether/hexane. Fractions with  $R_f$  of about 0.37 on evaporation gave 3-(1-chlorotridecyl)-2-trimethylsilylfuran as a pale yellow oil, solidified to a colorless solid on storage at -20°.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.26 (s, 9H), 0.89 (t, 3H,  $J=6.3$  Hz), 2.16 (brs, 20H), 1.85-2.05 (2m, 2H), 5.87 (t, 1H,  $J=7.5$  Hz), 6.63 (d, 1H,  $J=2.3$  Hz) and 7.66 (d, 1H,  $J=2.4$  Hz).

MS m/e (% abundance): 321 ( $M^+ - \text{Cl}$ , 57), 180 (14), 154 (43), 153 (16), 75 (13) and 73 (100).

A mixture of this intermediate and Rose Bengal in tetrahydrofuran is exposed to singlet oxygen at -78° for 2 hours. The solvent is removed and the residue purified (TLC) to give 4-(1-chlorotridecyl)-5-hydroxy-2-(5H)-furanone.

Treating the above prepared 5-hydroxyfuranone in tetrahydrofuran and methanol, with sodium borohydride by the procedure of Example 5 gives 4-(1-chlorotridecyl)-2(5H)-furanone.

45

#### Example 10

50

#### (E),(Z)-3-(1-Tridecenyl)-5-trimethylsilylfuran

n-Butyl lithium (a 1.6 M solution in hexane: 5.58 ml, 8.9 mmol) was added dropwise to a solution of dodecyltriphenylphosphonium bromide (4.57 g, 8.9 mmol) in tetrahydrofuran (35 ml) at 0° under argon. After 25 min., a solution of 5-trimethylsilyl-3-furaldehyde (1 g, 5.9 mmol) in tetrahydrofuran (3 ml) was added. Stirring was continued for 1 hour at 0° and the mixture was quenched with methanol/water (1:1, 60 ml). Extraction (hexane/ether, 1:1), washing (brine) and evaporation of the dried (magnesium sulphate) extracts gave an oil, which was purified by flash chromatography (silica) using 5% ethyl ether/hexane.

Fractions with  $R_f$  of about 0.8 on evaporation afforded the title olefin as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (E)-isomer: 0.31 (s, 9H), 0.92 (t, 3H,  $J = 7.1$  Hz), 1.30 (brs, 18H), 2.29 (q, 2H,  $J = 7.3$  Hz), 5.95, 6.00 (dt, 1H,  $J = 15.0$  Hz, 7.5 Hz), 6.25 (d, 1H,  $J = 15$  Hz), 6.68 (s, 1H) and 7.66 (s, 1H).

(Z)-isomer: 0.30 (s, 9H), 0.92 (t, 3H,  $J = 7.1$  Hz), 1.30 (brs, 18H), 2.15 (q, 2H,  $J = 7.3$  Hz), 5.55, 5.60 (dt, 1H,  $J = 11.5$  Hz, 5.5 Hz), 6.15 (d, 1H,  $J = 11.5$  Hz), 6.77 (s, 1H) and 7.58 (s, 1H). ((E):(Z) = 1:2)

MS m/e (% abundance): 320 ( $M^+$ , 38), 180 (25), 154 (50), 75 (15) and 73 (100).

#### 3-(1,2-Dihydroxytridecyl)-5-trimethylsilylfuran

Pyridine (31  $\mu\text{l}$ , 0.38 mmol), followed by osmium tetroxide (a 2.5% by weight solution in *tert*-butanol; 5 drops) was added to a solution of (E), (Z)-3-(1-trideceny)-5-trimethylsilylfuran (111 mg, 0.35 mmol) and N-methylmorpholine N-oxide (45 mg, 0.38 mmol) and acetone (2 ml) at room temperature. After stirring for 4 days, the mixture was acidified (dilute hydrochloric acid) and extracted thoroughly with ethyl acetate. The extracts were combined, dried (magnesium sulphate) and evaporated down to give an oil, which was flash chromatographed on silica using 60% ethyl ether/hexane. Fractions with  $R_f$  of about 0.26 and 0.21 (mixture of diastereomers) on evaporation gave the title diol as an off-white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (mixture of diastereomers): 0.26 (s, 3H), 0.88 (t, 3H,  $J = 6.5$  Hz), 1.26-1.60 (m, 2H), 3.55-3.85 (m, 1H), 4.45 (d, 1H), 4.65 (d, 1H), 6.60 (s, 1H), 6.66 (s, 1H) and 7.63 (s, 1H).

MS m/e (% abundance): 354 ( $M^+$ , 4), 339 (2), 321 (1), 171 (17), 170 (100), 169 (87), 153 (13), 98 (16), 75 (13), 73 (59), 57 (11) and 55 (12).

#### 3-(1,2-Diacetoxytridecyl)-5-trimethylsilylfuran

A mixture of 4-(1,2-dihydroxytridecyl)-5-trimethylsilylfuran (110 mg, 0.31 mmol), acetic anhydride (1.5 ml) and pyridine (1.5 ml) was stirred at room temperature for 13 hours. After most of the solvent was removed under high vacuum, the residue was dissolved in dichloromethane and washed thoroughly with aqueous copper sulphate. Evaporation of the dried (magnesium sulphate) organic phase gave an oil, which was purified by flash chromatography using 10% ethyl ether/hexane. Fractions with  $R_f$  of about 0.52 and 0.46 (mixture of diastereomers) on evaporation gave the title diacetate.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (mixture of diastereomers): 0.29, 0.30 (2s, 9H), 0.92 (t, 3H,  $J = 7.0$  Hz), 1.30 (br, 18H), 1.50 (m, 2H), 2.09, 2.10, 2.11, 2.12 (4s), 5.25 (m, 1H), 5.88 (d, 1H,  $J = 7.5$  Hz), 5.95 (d, 1H,  $J = 3.5$  Hz), 6.63 (s, 1H), 6.65 (s, 1H), 7.66 (s, 1H) and 7.67 (s, 1H).

MS m/e (% abundance): 438 ( $M^+$ , 2), 423 (2), 407 (2), 391 (6), 379 (100), 337 (16), 336 (23), 169 (23), 117 (13), 73 (16) and 61 (14).

#### 4-(1,2-Diacetoxytridecyl)-5-hydroxy-2(5H)-furanone

A mixture of 3-(1,2-diacetoxytridecyl)-5-trimethylsilylfuran (82 mg, 0.19 mmol) and Rose Bengal (5 mg) in tetrahydrofuran (7 ml) was exposed to singlet oxygen at  $-78^\circ$  for 3 hours. The residue, after solvent removal, was purified by preparative TLC (silica developed with 60% ethyl ether/hexane). The title furanone was obtained as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (mixture of diastereomers): 0.9 (t, 3H,  $J = 6.4$  Hz), 1.27 (brs, 18H), 1.65 (br, 2H), 2.10, 2.11, 2.17, 2.21 (4s, 12H), 5.21 (brt, 1H), 5.50-5.80 (2 brm, 2H), 6.03 (brs, 1H), 6.13 (brs, 1H) and 6.16 (brs, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 14.1, 20.6, 20.7, 20.9, 22.6, 25.2, 25.3, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8, 70.0, 72.7, 98.2, 120.5, 121.2, 161.2, 164.0, 170.1 and 171.2.

MS m/e: Exact mass calculated for  $\text{C}_{21}\text{H}_{38}\text{NO}_7$  ( $M + \text{NH}_4$ ) $^+$  416.2648, found 416.2652.

#### 4-(1,2-Diacetoxytridecyl)-2(5H)-furanone

By the procedure of Example 5, sodium borohydride is added to the above prepared hydroxyfuranone in tetrahydrofuran and methanol at room temperature. Stirring for two hours, then working up as in Example 6 gives the title furanone compound.

5

### Example 11

10

#### 4-[1-(2-Methoxyethoxy)methoxytridecyl]-2-trimethylsilylfuran

A mixture of 1-bromododecane (222 mg, 0.89 mmol) and magnesium turnings (22 mg, 0.94 mmol) in tetrahydrofuran (5 ml) was refluxed under argon for 1 hour. After cooling to 0°, a solution of 5-trimethylsilyl-3-furaldehyde (150 mg, 0.89 mmol) in tetrahydrofuran (1 ml) was added and conditions maintained for 1 hour. 2-Methoxyethoxymethyl chloride (0.15 ml, 1.34 mmol) was added and stirring was continued at room temperature for 16 hours. The mixture was quenched with water and extracted with ethyl ether. Evaporation of the dried (magnesium sulphate) extracts gave an oil, which was purified by preparative TLC (silica plate; developed with 15% ethyl ether/petroleum ether). The title trimethylsilylfuran was obtained as a pale yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.28 (s, 9H), 0.91 (t, 3H, J = 6.8 Hz), 1.28 (brs, 20H), 1.75 (m, 1H), 1.85 (m, 1H), 3.43 (s, 3H), 3.55 (m, 2H), 3.65 (m, 1H), 3.85 (m, 1H), 4.61 (t, 1H, J = 7.3 Hz), 4.68 (dd, 2H), 6.60 (s, 1H) and 7.58 (s, 1H).

MS m/e (% abundance): 426 (M<sup>+</sup>, 3), 322 (35), 321 (100), 249 (6), 154 (9) and 89 (16).

25

#### 4-[1-(2-Methoxyethoxy)methoxytridecyl]-5-hydroxy-2(5H)-furanone

A mixture of 4-[1-(2-methoxyethoxy)methoxytridecyl]-2-trimethylsilylfuran (150 mg, 0.35 mmol) and Rose Bengal (5 mg) in tetrahydrofuran (10 ml) was exposed to singlet oxygen for 2 hours at -78°. The residue, after solvent removal, was purified by preparative TLC (silica plate; developed with 70% ethyl ether/petroleum ether). The title furanone was obtained as a pale yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.91 (t, 3H, J = 6.4 Hz), 1.29 (s, 20H), 1.75 (brm, 2H), 3.37 (s, 3H), 3.40 (m, 2H), 3.66 (m, 2H), 3.85 (m, 1H), 4.28 (m, 1H), 4.80 (dd, 2H), 5.60 (br, 1H), 5.90 (brs, 1H) and 6.10 (brs, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 14.0, 22.6, 25.2, 29.6, 28.7, 28.8, 28.9, 29.1, 29.3, 29.4, 29.6, 31.8, 35.5, 58.7, 66.8, 71.3, 73.5, 96.1, 98.1, 98.8, 118.1 and 170.3.

MS m/e: Exact mass calculated for C<sub>21</sub>H<sub>42</sub>NO<sub>6</sub> (M + NH<sub>4</sub>)<sup>+</sup> 404.3012, found 404.2997.

40

#### 4-[1-(2-methoxyethoxy)methoxytridecyl]-2(5H)-furanone

Treating the above prepared hydroxyfuranone with sodium borohydride by the procedure of Example 5 gives the title furanone.

45

### Example 12

50

#### 4-(1-O-Carboethoxytridecyl)-2-trimethylsilylfuran

A mixture of 1-bromodecane (81 mg, 0.33 mmol) and magnesium turnings (8 mg, 0.33 mmol) in THF (1.0 ml) was refluxed under nitrogen for 30 minutes. After cooling to 0°, a solution of 5-trimethylsilyl-3-furaldehyde (50 mg, 0.30 mmol) in tetrahydrofuran (0.5 ml) was added. The solution was stirred for one hour while the cooling bath warmed to room temperature. Ethylchloroformate (64 mg, 0.59 mmol) was

added and the solution stirred at room temperature until no starting material remained (as monitored by TLC). The mixture was quenched with water and the organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by preparative TLC (silica plate; developed with 5% ethyl ether/hexane). The titled compound was obtained as a colorless oil.

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.64 (s, 1H),  $\delta$  6.62 (s, 1H), 5.6 (t,  $J=7.5$  Hz, 1H),  $\delta$  4.16 (m, 2H),  $\delta$  1.9 (m, 1H),  $\delta$  1.8 (m, 1H),  $\delta$  1.26 (m, 23H),  $\delta$  0.85 (t,  $J=7.5$  Hz, 3H),  $\delta$  0.25 (s, 9H).

#### 4-(1-O-Carboethoxytridecyl)-5-hydroxy-2(5H)-furanone

10

A mixture of 4-(1-O-carboethoxytridecyl)-2-trimethylsilylfuran (43.3 mg, 0.10 mmol) and Rose Bengal (5 mg) in THF (5 ml) was exposed to singlet oxygen at  $-78^\circ$  for four hours. The residue, after solvent removal, was purified by preparative TLC (silica plate; developed with 60% ethyl ether/hexane). The title furanone

15 was obtained as a white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.25 (s, 1H),  $\delta$  6.08 (s, 1H),  $\delta$  6.02 (s, 1H),  $\delta$  5.35 (m, 2H),  $\delta$  4.2 (m, 2H),  $\delta$  1.84 (m, 2H),  $\delta$  1.35 (m, 23H),  $\delta$  0.85 (t,  $J=7.5$ , 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 170, 169.6, 166.6, 165.9, 155, 154.9, 119.4, 118.7, 97.9, 97.7, 76.5, 72.9, 72.8, 65, 64.7, 33.3, 33.1, 31.9, 29.5, 29.4, 29.3, 29.1, 24.9, 24.8, 22.6, 14.0.

20 MS m/e: Exact mass calculated for  $\text{C}_{17}\text{H}_{28}\text{O}_3$  280.2038 ( $\text{M}^+$ ), found 280.2046.

#### 4-(1-O-Carboethoxytridecyl)-2(5H)-furanone

25

Treating the above prepared hydroxyfuranone with sodium borohydride by the procedure of Example 6 gives the title furanone.

30

#### Example 13

#### 4-Tridecyl-5-hydroxy-2(5H)-furanone

35

A mixture of (E), (Z)-4-(1-tridecenyl)-2-trimethylsilylfuran (2.0 g, 6.25 mmol) and 10% palladium or carbon (20 mg) in ethyl ether (10 ml) was hydrogenated at room temperature for 7h. The mixture was filtered through celite and the filtrate upon evaporation gave essentially pure 4-tridecyl-2-trimethylsilylfuran.

40 The silylfuran was redissolved in tetrahydrofuran (8 ml) and was exposed to singlet oxygen, in the presence of Rose Bengal (5 mg), for 2h at  $0^\circ$ . The residue, after solvent removal, was purified by a silica column using 60% ethyl ether/hexane to give the titled furanone.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.90 (t, 3H), 1.25 (brs, 20H), 1.60 (m, 2H), 2.50 (m, 2H), 4.0 (brd, 1H), 5.85 (brs, 1H) and 6.05 (brd, 1H).

45 LRMS (m/e, % abundance) 283 ( $\text{M} + \text{H}^+$ , 26), 282 ( $\text{M}^+$ , 37), 264 (14), 253 (11), 236 (20), 235 (11), 205 (10), 204 (12), 165 (15), 152 (19), 151 (23), 138 (34), 137 (37), 124 (25), 123 (30), 114 (26), 110 (39), 98 (58), 97 (76), 96 (61), 95 (50) and 81 (61).

50

#### 4-Tridecyl-2(5H)-furanone

Sodium borohydride (29.5 mg, 0.78 mmol) was added portionwise to a solution of 4-tridecyl-5-hydroxy-2(5H)-furanone (218.5 mg, 0.78 mmol) in methanol (1 ml) and tetrahydrofuran (5 ml) at room temperature.

55 After 6h at room temperature, most of the solvent was removed and the residue was acidified with dilute hydrochloric acid. Extraction (ethyl acetate) and evaporation of the dried (magnesium sulfate) extracts gave an oil, which was purified by a silica column using 30% ethyl ether/hexane. Fractions with  $R_f$  of about 0.14 on evaporation gave the titled furanone.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.88 (t, 3H, J=7.0 Hz), 1.26 (brs, 20H), 1.60 (m, 2H), 2.40 (t, 2H, J=8.0 Hz), 4.73 (brs, 2H) and 5.84 (t, 1H, J=1.6 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 13.8, 22.4, 26.9, 28.3, 28.9, 29.1, 29.2, 29.3, 29.5, 31.6, 72.9, 115.3, 171.0 and 174.4.

HRMS exact mass calculated for C<sub>17</sub>H<sub>30</sub>O<sub>2</sub>(M<sup>+</sup>) 266.2245, found 266.2245.

5

#### Example 14

10 Reacting 4-(1-hydroxytridecyl)-2(5H)-furanone with diethyl chlorophosphate give 4-(1-diethylphosphonyl)tridecyl-2(5H)-furanone.

#### Example 15

15

Reacting 4-(1-diethylphosphonyl)tridecyl-2(5H)-furanone with bromotrimethylsilane gives 4-(1-phosphonyl)tridecyl-2(5H)-furanone.

20

#### Example 16

25 Reacting 4-(1-hydroxytridecyl)-2-triethylsilylfuran with diphenylphosphonyl azide and diethyl azidocarboxylate gives 4-(1-azidotridecyl)-2-triethylsilylfuran. Reducing this azide with lithium aluminum hydride gives 4-(1-aminotridecyl)-2-triethylsilylfuran. Acetylation of this intermediate with acetic anhydride gives 4-(1-acetamide)tridecyl-2-triethylsilylfuran. Oxidizing this amide with oxygen using Rose Bengal as an initiator gives 4-(1-acetamido)-5-hydroxy-2(5H)-furanone. Reduction of this furanone with sodium borohydride gives 4-(1-acetamide)-2(5H)-furanone.

30

#### Example 17

35 Reacting 4-(1-aminotridecyl)-2-triethylsilylfuran with methanesulfonyl chloride gives 4-(1-methanesulfonylamide)-2-triethylsilylfuran. Oxidizing this sulfonamide with oxygen using Rose Bengal as an initiator gives 4-(1-methanesulfonylamide)-5-hydroxy-2(5H)-furanone. Reduction of this furanone gives 4-(1-methanesulfonylamido)-5-hydroxy-2(5H)-furanone.

40

#### Example 18

45 As in example 17, but substituting methanesulfonyl chloride with chlorosulfonyl isocyanate and carry through the reaction sequence gives 4-(1-ureidotridecyl)-2(5H)-furanone.

#### Example 19

50

The following test procedures may be used to demonstrate activity of the compounds of this invention:

#### Calcium Channel (mobilization) Inhibition Assay

55

Polymorphonuclear leukocytes (PMNa), gastric glands, GH<sub>3</sub> cells, A431 cells, spleen cells, human keratinocytes corneal cells, etc. were loaded with the Ca<sup>2+</sup> sensitive fluorescent dye, Fura-2. The appropriate cell type was chosen and the potency and efficacy of the anti-inflammatory furanones on calcium

mobilization, calcium channel inhibition quantitated. The methods used for A431 cells listed below are representative of those used for other cells.

A431 cells were detached using a 5-10 min trypsin-EDTA treatment whereas GH<sub>3</sub> cells were treated 2 to 5 min with a 1% pancreatin solution. Cells were immediately washed twice in a 20mM HEPES buffer (pH 7.4) containing 120mM NaCl, 6 mM KCl, 1 mM MgSO<sub>4</sub>, 1 mg/ml glucose and 1 mg/ml pyruvate and 1.4mM calcium (medium A). Approximately 5 x 10<sup>6</sup> cells were suspended in medium A and incubated with 4μM fura-2-AM for 15 min at 37°C.

After washing the fura-2 loaded cells, the uptake of dye was checked using fluorescence microscopy and found to be evenly distributed in the cytosol of all cells. Fluorescence was continuously recorded with a Perkin-Elmer LS-5 spectrofluorometer. The excitation wavelength was set at 340nm and emission wavelength set at 500nm. The cell suspension was continually stirred, maintained at 37°C and equilibrated for approximately 5 min before addition of various agents. [Ca<sup>2+</sup>]<sub>i</sub> was calculated using the following formula:

$$[Ca^{2+}]_i = \frac{F - F_{min}}{F_{max} - F}$$

All fluorescence values were measured relative to a EGTA-quenched signal determined as follows: F was the relative fluorescence measurement of the sample. F<sub>max</sub> was determined by lysing the cells with digitonin (100μg/ml) in DMSO. After F<sub>max</sub> was determined the pH was adjusted to 8, with NaOH and Ca<sup>2+</sup> chelated with 3mM EGTA to totally quench the fura-2 signal and obtain F<sub>min</sub>.

When quin-2 was used, cells were incubated with 10μM quin-2 at 37°C for 1 hr, washed and then used.

#### Mouse Ear Anti-Inflammatory Assay

Test compound and phorbol myristate acetate (PMA) are topically applied simultaneously to the pinnae of the left ears of mice. PMA alone is applied to the right ear. Three hours and 20 minutes after application, the mice are sacrificed, left and right ears removed, and standard sized bores taken. Edema (inflammation) is measured as the difference in weight between left and right ears [Van Arman, C.G., Clin Pharmacol Ther (1974) 16:900-904].

Compounds of this invention demonstrate weak or no activity in the following test procedures:

#### Inhibition of Phospholipase A<sub>2</sub>

The effect of compounds of this invention on bee venom phospholipase A<sub>2</sub> is determined by the following procedure:

- a. Bee venom phospholipase A<sub>2</sub> in 10 μM HEPES (pH 7.4) with 1 mM CaCl<sub>2</sub> is incubated with vehicle or test agent for 1.0 hour at 41°C.
- b. 1.36 mM phosphatidylcholine, 2.76 mM Triton X-100 are dispersed in buffer by sonication and then mixed with L-3 phosphatidylcholine, 1-palmitoyl-2-(1-<sup>14</sup>C) palmitoyl for 10 min.
- c. Start the reaction by the addition of enzyme (0.495 units/ml).
- d. Incubation for 15 sec. at 41°C.
- e. Reaction is terminated by addition of 2.5 ml of isopropanol: n-heptane: 0.5 M H<sub>2</sub>SO<sub>4</sub> (40:10:1; v:v:v).
- f. 2.0 ml n-heptane and 1.0 ml H<sub>2</sub>O added; mixture centrifuged.
- g. 2.0 ml n-heptane removed and treated with 200-300 mg of silica gel HR60.
- h. Samples centrifuged; 1 ml of n-heptane SN removed and added to 10 ml scintillation fluid.
- i. Samples counted on a scintillation counter.

#### Inhibition of Phosphoinositide-specific Phospholipase C

The effect of compounds of this invention on phosphoinositide-specific phospholipase C may be



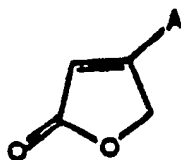
determined by procedures described by Bennett et al, Molecular Pharmacology 32:587-593 (1987).

# Claims

5

1. A compound of the formula (I):

10



(I)

15 in which:

A is  $C_8-C_{20}$ alkyl or  $CH(R_1)R_2$ ;

R is  $C_7-C_{20}$ alkyl;

$R_1$  is hydroxy,  $OCOR_2$ , 2-(methoxy)ethoxymethoxy, halogen and  $NHR_3$ ;

$R_3$  is H,  $C_1-C_6$  alkanoyl,  $COCF_3$  and  $C_1-C_6$  sulfonyl;

20  $R_2$  is  $C_1-C_{14}$ alkyl or amino optionally N-substituted by one  $\alpha$ -( $C_1-C_4$ alkyl)benzyl group, by one or two  $C_1-C_4$ alkyl groups or by one phenyl group; or  $OP(R_4R_5)$ ; or

R is 2-(methoxy)ethoxymethoxymethyl and  $R_1$  is  $OCO-(C_7-C_{14}$ alkyl); or

R is  $CH(OCOC_1-C_4alkyl)C_7-C_{20}alkyl$  and  $R_1$  is  $OCO(C_1-C_4alkyl)$ ; and

$R_4 = R_5$  is H or  $C_1-C_4$  alkyl.

25 2. A compound of claim 1 in which:

A is  $-CH(R_1)R_2$ ;

R is  $C_7-C_{20}$ alkyl;

$R_1$  is hydroxy or  $OCOR_2$ ;

$R_2$  is  $C_1-C_{14}$ alkyl or  $\alpha$ -methylbenzylamino; or

30 R is 2-(methoxy)ethoxymethoxymethyl and  $R_1$  is  $OCO-(C_7-C_{14}alkyl)$ .

3. A compound of claim 1 which is selected from

4-[1-dodecanoyloxy-2-(2-methoxyethoxy)methoxymethyl]-2(5H)-furanone,

4-(1-acetoxytridecyl)-2(5H)-furanone,

4-[1-((R)-(+)- $\alpha$ -methylbenzylcarbamoyl)tridecyl]-2(5H)-furanone, and

35 4-(1-hydroxytridecyl)-2(5H)-furanone.

4. A pharmaceutical composition which comprises a pharmaceutical carrier and a therapeutically effective amount of a compound of any one of claims 1 to 3.

5. A pharmaceutical composition of claim 4 having an anti-inflammatory activity in mammals.

40 6. A compound according to any one of claims 1 to 3 for use in the treatment of inflammation or an allergic response in a mammal.

7. A compound according to any one of claims 1 to 3 for use in the treatment of psoriasis in a mammal.

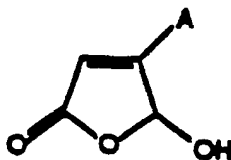
8. The use of a compound according to any one of claims 1 to 3 in the preparation of a medicament for the treatment of inflammation or an allergic response in a mammal.

45 9. The use of a compound according to any one of claims 1 to 3 in the preparation of a medicament for the treatment of psoriasis in a mammal.

10. A process for the preparation of a compound of the formula (I) as defined in any one of claims 1 to 3, which process comprises:

(i) the reduction of a compound of the formula:

50



55

or,

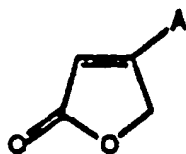
(ii) when it is required to prepare a compound of the formula (I) wherein  $R_1$  is  $OCOR_2$ , the acylation of the corresponding compound wherein  $R_1$  is hydroxy.

Claims for the following Contracting States: ES, GR

5

1. A process for the preparation of a compound of the formula (I):

10



(I)

15 in which:

A is  $C_8-C_{20}$ alkyl or  $CH(R_1)R_2$ ;

R is  $C_7-C_{20}$ alkyl;

$R_1$  is hydroxy,  $OCOR_2$ , 2-(methoxy)ethoxymethoxy, halogen and  $NHR_3$ ;

$R_3$  is H,  $C_1-C_6$  alkanoyl,  $COCF_3$  and  $C_1-C_6$  sulfonyl;

20  $R_2$  is  $C_1-C_{14}$ alkyl or amino optionally N-substituted by one  $\alpha$ -( $C_1-C_4$ alkyl)benzyl group, by one or two  $C_1-C_4$ alkyl groups or by one phenyl group; or  $OP(R_4R_5)$ ; or

R is 2-(methoxy)ethoxymethoxymethyl and  $R_1$  is  $OCO-(C_7-C_{14}$ alkyl); or

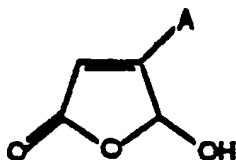
R is  $CH(OCOC_1-C_4alkyl)C_7-C_{20}alkyl$  and  $R_1$  is  $OCO(C_1-C_4alkyl)$ ; and

$R_4 = R_5$  is H or  $C_1-C_4$  alkyl;

25 which process comprises:

(i) the reduction of a compound of the formula

30



35

or,

(ii) when it is required to prepare a compound of the formula (I) wherein  $R_1$  is  $OCOR_2$ , the acylation of the corresponding compound wherein  $R_1$  is OH.

2. A process of claim 1 wherein:

40

A is  $-CH(R_1)R_2$ ;

R is  $C_7-C_{20}$ alkyl;

$R_1$  is hydroxy or  $OCOR_2$ ;

$R_2$  is  $C_1-C_{14}$ alkyl or  $\alpha$ -methylbenzylamino; or

R is 2-(methoxy)ethoxymethoxymethyl and  $R_1$  is  $OCO-(C_7-C_{14}alkyl)$ .

45

3. A process of claim 1 wherein the compound of the formula (I) is selected from::

4-[1-dodecanoyloxy-2-(2-methoxyethoxy)methoxymethyl]-2(5H)-furanone,

4-(1-acetoxytridecyl)-2(5H)-furanone,

4-[1-((R)-(+)- $\alpha$ -methylbenzylcarbamoyl)tridecyl]-2(5H)-furanone, and

4-(1-hydroxytridecyl)-2(5H)-furanone.

50

4. A process according to any of the preceding claims wherein the reduction is effected using a reducing agent such as sodium borohydride.

5. A process for the preparation of a pharmaceutical composition containing a compound of the formula (I) as defined in any one of claims 1 to 3 and a pharmaceutically acceptable carrier, which process comprises bringing the compound of the formula (I) into association with the pharmaceutically acceptable carrier.

55

6. A process of claim 4 wherein the pharmaceutical composition has anti-inflammatory activity in mammals.

7. The use of a compound of the formula (I) as defined in any one of claims 1 to 3 in the preparation of

a medicament for the treatment of inflammation or an allergic response in a mammal.

8. The use of a compound of the formula (I) as defined in any one of claims 1 to 3 in the preparation of a medicament for the treatment of psoriasis in a mammal.

5

10

15

20

25

30

35

40

45

50

55